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Alcohol drinking and primary liver cancer: a pooled analysis of four Japanese cohort studies

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Because studies of the association between alcohol intake and the risk of primary liver cancer use varying cut-off points to classify alcohol intake, it is difficult to precisely quantify this association by meta-analysis of published data. Furthermore, there are limited data for women in prospective studies of the dose-specific relation of alcohol intake and the risk of primary liver cancer. We analyzed original data from 4 population-based prospective cohort studies encompassing 174,719 participants (89,863 men and 84,856 women). After adjustment for a common set of variables, we used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of primary liver cancer incidence according to alcohol intake. We conducted a meta-analysis of the HRs derived from each study. During 1,964,136 person-years of follow-up, 804 primary liver cancer cases (605 men and 199 women) were identified. In male drinkers, the multivariate-adjusted HRs (95% CI) for alcohol intakes of 0.1–22.9, 23.0–45.9, 46.0–68.9, 69.0–91.9 and ≥92.0 g/day, as compared to occasional drinkers, were 0.88 (0.57–1.36), 1.06 (0.70–1.62), 1.07 (0.69–1.66), 1.76 (1.08–2.87) and 1.66 (0.98–2.82), respectively (p for trend = 0.015). In women, we observed a significantly increased risk among those who drank ≥23.0 g/day, as compared to occasional drinkers (HR: 3.60; 95% CI: 1.22–10.66). This pooled analysis of data from large prospective studies in Japan indicates that avoidance of (1) heavy alcohol drinking (≥69.0 g alcohol/day) in men and (2) moderate drinking (≥23.0 g alcohol/day) in women may reduce the risk of primary liver cancer.

In 2007, the International Agency for Research on Cancer stated that alcoholic beverages are "carcinogenic to humans" (Group 1) and concluded that the occurrence of primary liver cancer was causally related to alcohol intake.[1] This conclusion was bolstered by a systematic review of epidemiologic studies of Japanese, which concluded that there was "convincing" evidence that alcohol drinking increases the risk of primary liver cancer.[2] However, several issues remain to be clarified. First, due to the use of differing cut-points for alcohol intake in previous studies, it is not possible to conduct a meta-analysis of published data to precisely quantify associations between alcohol intake and the risk of primary liver cancer. Second, evidence from prospective cohort studies of women is limited and inconsistent.[3–6] There is a high

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incidence of hepatocellular carcinoma (HCC) in East Asia,[7] and, in Japan, HCC accounts for more than 90% of primary liver cancers.[8] Japan is unique among East Asian countries, however, because hepatitis C virus (HCV) infection is the predominant risk factor for HCC: 70% and 15% of HCCs are attributable to HCV and hepatitis B virus (HBV), respectively.[8] Indeed, the HCV-dominant pattern in Japan is similar to that of the United States,[9] where the incidence of HCC is increasing.[10] Thus, it is worthwhile to present pooled data for Japan because of the distinctive etiological characteristics of HCC in that country. To examine these issues in detail, we conducted a pooled analysis of data from 4 large-scale cohort studies performed in Japan.

Material and Methods

Study population

In 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan began pooling original data from major cohort studies to evaluate the association between lifestyle and major cancers in Japanese, along with systematic reviews of the relevant literature.[11] Topics for the pooled analysis were determined based on their scientific and public health importance, as determined by discussions among authors.[12,13] The following *a priori* inclusion criteria were established for the present analysis: population-based cohort studies conducted in Japan, study initiation between the mid-1980s and mid-1990s, inclusion of more than 30,000 participants, baseline collection of information on diet and amount of alcohol intake (g/day) using a validated questionnaire or similar method and collection of incidence data for primary liver cancer during the follow-up period. We identified three ongoing studies that met these criteria: (1) The Japan Public Health Center-based prospective Study (JPHC),[14] (2) The Japan Collaborative Cohort Study (JACC)[15] and (3) The Miyagi Cohort Study (MIYAGI).[16] The JPHC was treated as 2 independent studies (JPHC I and JPHC II) due to the use of different dietary questionnaires. Thus, data from a total of 4 studies were analyzed. We excluded participants with a history of cancer at baseline or missing information on alcohol intake. Selected characteristics of these studies are summarized in Table 1.

Findings regarding the association between alcohol intake and primary liver cancer risk in each cohort have been reported.[5,17–19] In this analysis, we used updated datasets, with longer follow-up periods, for the JPHC and MIYAGI. For the JACC, we updated the datasets using incidence data for primary liver cancer because previous reports on the current topic analyzed primary liver cancer mortality only.[5,18] Each study obtained approval from the relevant institutional ethical review boards, namely, those of the National Cancer Center (JPHC I and JPHC II), Nagoya University (JACC) and Tohoku University Graduate School of Medicine (MIYAGI).

Exposure assessment

In each study, alcohol drinking status was assessed by using self-administered questionnaires at baseline. Although the wording of the questions varied among studies, each study calculated alcohol intake in grams of ethanol/day as a continuous measure for regular drinkers. Because there were no data on the beverage-specific frequency of alcohol consumption, alcohol intake was calculated by multiplying average frequency by total alcohol intake from each type of beverage on a single occasion. In Japan, the *go* is the most commonly used unit for measuring the amount of alcohol intake; 1 *go* of *sake* (rice wine) is equivalent to 180 ml and contains approximately 23 g of ethanol.

Participants in JPHC I were asked about the average frequency, using six categories (<1 day/month, 1–3 days/month, 1–2 days/week, 3–4 days/week, 5–6 days/week and daily). Participants consuming alcoholic beverages at least once a week were also asked to identify the type and average intake of each beverage consumed. Participants in JPHC II were asked about drinking status, i.e., never-, ex-, or current drinking. Ex- and current drinkers provided information on average frequency, using four categories (1–3 days/month, 1–2 days/week, 3–4 days/week and almost daily), beverage type and average intake of each beverage type. For JPHC I and JPHC II, the amount of ethanol in each type of beverage was calculated as follows: 1 *go* of *sake* equals 23 g ethanol, 1 *go* of *shochu* or *awamori* (white spirits) equals 36 g, 633 ml of beer equals 23 g, 30 ml of whiskey or brandy equals 10 g and 60 ml of wine equals 6 g. The questionnaires in JACC and MIYAGI assessed alcohol consumption by first asking if the participant was a never-, ex-, or current drinker. Current drinkers were then asked about average frequency of drinking, using four categories (<once/week, 1–2 days/week, 3–4 days/week and almost daily), the beverage usually consumed and the amount consumed on one occasion. The total amount consumed on one occasion was converted by respondents into the corresponding *go* equivalent of sake. The questionnaires included information on the amount of each alcoholic beverage that contained the same quantity of ethanol as 1 *go* of sake and the participants were asked to refer to this guide when recording the total amount consumed on a single occasion: the alcohol content of 1 *go* of *sake* equals that of approximately 663 ml of beer, 1 *go* of wine, 1.5 *go* of *shochu*, or 2 measures of spirits.

Intake was divided into categories by using identical cut-points across the studies. The categories were nondrinkers (never- and ex-drinker), occasional drinkers (<once/week) and regular drinkers (≥once/week: 0.1–22.9, 23.0–45.9, 46.0–68.9, 69.0–91.9, or ≥92.0 g/day for men; 0.1–22.9 or ≥23.0 g/day for women). Correlation coefficients between alcohol intakes estimated from the questionnaire and those from dietary records were 0.77 in men and 0.55 in women for the JPHC[20] and 0.77 in men and 0.71 in women for the MIYAGI.[21] The JACC, for which information on the

Table 1. Characteristics of cohort studies included in pooled analysis

Study	Population	Age range at baseline, y	Year of baseline survey	Population size	Response rate (%) for baseline questionnaire (%)	Method of follow-up	Present pooled analysis							
							Age range, y	Last Follow-up	Mean follow-up period, y	Outcome	Size of cohort		No. of cancer cases	
											Men	Women	Men	Women
JPHC I	Japanese residents of five public health-center areas in Japan	40–59	1990	61,595	82%	Cancer registry and death certificate	40–59	2004	13.6	Incidence	19,847	21,526	95	31
JPHC II	Japanese residents of 6 public health-center areas in Japan	40–69	1993–1994	78,825	80%	Cancer registry and death certificate	40–69	2004	10.5	Incidence	27,565	31,786	263	85
JACC	Residents of 45 areas throughout Japan	40–79	1988–1990	110,792	83%	Cancer registry (selected areas: 22) and death certificate	40–79	2001	10.4	Incidence	21,804	31,544	156	83
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47,605	92%	Cancer registry and death certificate	40–64	2001	11.0	Incidence	20,647	18,385[1]	91	19[1]
Total											89,863	84,856	605	199

Abbreviations: JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study.
[1]Not included in main analysis.

validation of alcohol intake was not available, used the same questions on alcohol intake as the MIYAGI.

The baseline questionnaires also asked about smoking status, history of diabetes mellitus and coffee intake. Information on history of liver disease was obtained using the question, "Has a doctor ever told you that you have any of the following diseases: chronic hepatitis/liver cirrhosis (yes/no)?" on the JPHC I and JPHC II and the question, "Have you ever had any of the following diseases: liver disease (hepatitis, etc.)?" on the JACC and MIYAGI. A history of liver disease was defined as a positive response to these questions.

Case ascertainment

Participants were followed from the baseline survey (JPHC I: 1990, JPHC II: 1993–1994, JACC: 1988–1990, MIYAGI: 1990) until the final date of follow-up for incidence in each study (JPHC I: 2004, JPHC II: 2004, JACC: 2001, MIYAGI: 2001). In each study, residence status, including survival, was confirmed by examining the residential registry. Information on cancer diagnosis was collected for the entire population in the JPHC I, JPHC II and MIYAGI; cases were identified by active patient notification from major local hospitals and/or examination of population-based cancer registries. In the JACC, information on cancer diagnosis was collected in only 22 of 45 study areas. Therefore, we used data only from those areas. Cases were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).[22] Each study also collected information on cause of death from death certificates and coded it according to the International Classification of Diseases and Health Related Problems, Tenth Revision (ICD-10),[23] which was used to complement hospital and registry data on cancer diagnosis. The study outcome was defined as incidence of primary liver cancer (ICD-O-3: C22.0; ICD-10: C22.0) during the follow-up period of each study.

Statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey for each study until the date of diagnosis of primary liver cancer, migration from the study area, death, or end of follow-up, whichever came first. Each study used Cox proportional hazards models to estimate sex-specific hazard ratios (HRs) and their 95% confidence intervals (CIs) of primary liver cancer for each alcohol intake category. We assumed that occasional drinkers would have the lowest risk of primary liver cancer because never-drinkers might include participants who may have stopped drinking due to ill health and because participants who were able to drink some alcohol but nevertheless consumed the lowest amount of alcohol would have the lowest risk of primary liver cancer. We therefore used occasional drinkers as the reference category. All analyses were performed after adjustment for age at baseline (years, continuous), geographic area within the study area (for JPHC I, JPHC II and JACC), smoking status (never-smoker, past smoker, current smoker of 1–19 cigarettes/day, or current smoker of $\geq$20 cigarettes/day in men; never-smoker, past smoker, or current smoker in women), history of diabetes mellitus (yes or no) and coffee intake (almost never, less than one cup/day, 1 or more cups/day). The linearity assumption between age at baseline and primary liver cancer risk in each cohort was tested graphically and accepted. These covariates were selected based on previous reports.[24–26] SAS Version 9.1 (SAS Institute, Cary, NC) was used for these calculations. A random effects model, which considers both within-study and between-study variation,[27] was used to obtain a single pooled estimate of the HRs, along with standard error for the HRs, from the individual studies for each category. Study-specific HRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. After exclusion of non-drinkers, the trend association was assessed in a similar manner: each study calculated the regression coefficient per 10-g increase in alcohol intake and its standard error from the Cox models, with alcohol intake in occasional drinkers defined as zero. Then, these values from individual studies were combined using a random effects model. We used Q-statistics to test for heterogeneity among studies.[27] Stata Version 9.2 (Stata Corporation, College Station, TX) statistical software was used for the simple pooled meta-analysis. All reported p-values are two-tailed.

The HRs of primary liver cancer in ex-drinkers and never drinkers are presented separately because these data were available in the JACC, MIYAGI and JPHC II. In men, we also conducted (1) an analysis stratified by history of liver disease, because previous studies indicated that the presence of chronic liver disease at baseline results in decreased alcohol consumption,[28,29] which might lead to underestimation of primary liver cancer risk[30] and (2) analyses excluding participants who received a diagnosis of liver disease in the first 3 years of follow-up. As for women, because there were no cases of primary liver cancer among occasional drinkers in the MIYAGI, we pooled data from the other 3 cohorts. To determine how this exclusion of the MIYAGI could alter the magnitude of the observed HRs, we conducted a sensitivity analysis in which we assumed one primary liver cancer case occurred in a randomly selected female occasional drinker in the MIYAGI. Then we calculated study-specific HRs and conducted the meta-analysis. We repeated this procedure 10 times. We also conducted analyses of a quadratic model that included a quadratic term for alcohol consumption (per 10 g/day) as well as a linear term. We used the Wald chi-square test to assess the statistical significance of the quadratic term.

Results

Our study included 174,719 participants (89,863 men and 84,856 women) and 804 primary liver cancer cases (605 men and 199 women) during 1,964,136 person-years of follow-up (Table 1). Approximately 50% of men habitually consumed $\geq$23.0 g/day of alcohol. In contrast, only 3% of women consumed this much alcohol per day.

Table 2. Results of pooled analysis (random effect model) of liver cancer incidence according to alcohol drinking status in men, 1988–2004

	Nondrinkers	Occasional drinkers (<once/week)	Current drinkers, alcohol intake (g/day)					Alcohol intake as a continuous variable (per 10 g/day)[1]		
			0.1–22.9	23.0–45.9	46.0–68.9	69.0–91.9	≥ 92.0	HR	*p* for trend	*p* for heterogeneity
All participants										
No. of cases	228	29	82	107	76	54	29			
No. of participants	21,207	6,570	17,802	19,158	15,054	6,735	3,337			
Person-years	227,464	76,313	197,262	212,688	169,582	76,987	37,826			
Age, area-adjusted HR (95% CI)	1.69 (1.14–2.51)	1.00 (Reference)	0.88 (0.57–1.36)	1.13 (0.75–1.72)	1.16 (0.75–1.80)	1.98 (1.22–3.23)	1.91 (1.13–3.23)	1.03 (1.01–1.05)	0.006	0.294
Multivariate-adjusted HR[1] (95% CI)	1.70 (1.15–2.53)	1.00 (Reference)	0.88 (0.57–1.36)	1.06 (0.70–1.62)	1.07 (0.69–1.66)	1.76 (1.08–2.87)	1.66 (0.98–2.82)	1.02 (1.004–1.04)	0.015	0.580
Excluding cases diagnosed in first 3 years of follow-up										
No. of cases	167	18	65	85	64	45	21			
Multivariate-adjusted HR[2] (95% CI)	1.88 (1.17–3.04)	1.00 (Reference)	1.04 (0.62–1.75)	1.24 (0.75–2.05)	1.36 (0.81–2.30)	2.18 (1.24–3.86)	1.78 (0.95–3.35)	1.02 (1.01–1.04)	0.012	0.686

[1]Trend association was assessed after exclusion of nondrinkers. Alcohol intake in occasional drinkers was defined as zero. [2]Multivariate-adjusted HR was adjusted for geographic area (in the JPHC I, JPHC II and JACC), age (continuous), history of diabetes mellitus (yes, or no), smoking status (never, past, current smoking 1-19 cigarettes/d, and ≥20 cigarettes/d), and coffee intake (almost never, <1 cup/day, ≥1 cup/day). Abbreviations: HR, hazard ratio; CI, confidence interval; JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study.

Table 3. Results of pooled analysis (random effect model) of liver cancer incidence according to alcohol drinking status in women, 1988–2004

	Nondrinkers	Occasional drinkers (<once/week)	Current drinkers, alcohol intake (g/day)		Alcohol intake as a continuous variable (per 10 g/day)[1]		
			0.1–22.9	≥ 23.0	HR	*p* for trend	*p* for heterogeneity
No. of cases	175	7	8	9			
No. of participants	66,691	7,366	8,613	2,186			
Person-years	763,638	85,452	93,487	23,437			
Age, area-adjusted HR (95% CI)	1.50 (0.69–3.25)	1.00 (Reference)	0.88 (0.25–3.05)	4.09 (1.40–11.90)	1.17 (1.01–1.35)	0.032	0.134
Multivariate-adjusted HR[2] (95% CI)	1.50 (0.69–3.25)	1.00 (Reference)	0.86 (0.26–2.88)	3.60 (1.22–10.66)	1.11 (0.96–1.29)	0.165[3]	0.248

[1]Trend association was assessed after exclusion of nondrinkers. Alcohol intake in occasional drinkers was defined as zero. [2]Multivariate-adjusted HR was adjusted for geographic area (in the JPHC I, JPHC II and JACC), age (continuous), history of diabetes mellitus (yes or no), smoking (never-smoker, past smoker or current smoker), and coffee intake (almost never, <1 cup/day, ≥1 cup/day). [3]The p value for the quadratic term of alcohol intake as a continuous variable (per 10 g/day) was 0.049 and was obtained by adding the relevant variable to the model including the linear term. Abbreviations: HR, hazard ratio; CI, confidence interval; JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study.

Table 2 shows the association between alcohol intake and risk of primary liver cancer in men. We found a U-shaped association between alcohol intake and primary liver cancer risk. In male drinkers, alcohol intake was dose-dependently associated with the risk of primary liver cancer: the multivariate-adjusted HRs (95 % CI) of primary liver cancer as compared to occasional drinkers were 0.88 (0.57–1.36), 1.06 (0.70–1.62), 1.07 (0.69–1.66), 1.76 (1.08–2.87) and 1.66 (0.98–2.82) for 0.1–22.9, 23.0–45.9, 46.0–68.9, 69.0–91.9 and ≥92.0 g/day, respectively (p for trend = 0.015). The test for heterogeneity across studies was not statistically significant for the HR per 10-g/day increase in alcohol intake (p = 0.580). We found an increased risk in nondrinkers as compared to occasional drinkers (multivariate-adjusted HR: 1.70; 95% CI: 1.15–2.53). Using data from the JACC, MIYAGI and JPHC II, the multivariate-adjusted HRs in ex-drinkers and never drinkers as compared to occasional drinkers were 3.30 (2.02–5.39) and 1.32 (0.82–2.12), respectively. The results were essentially unchanged when cases diagnosed in the first 3 years of follow-up were excluded.

As for women, because there were no cases of primary liver cancer among occasional drinkers in the MIYAGI, we pooled data from the other 3 cohorts. Drinkers who consumed ≥23.0 g/day of alcohol had a significantly increased risk of primary liver cancer as compared to occasional drinkers (multivariate-adjusted HR: 3.60; 95% CI: 1.22–10.66; Table 3). The multivariate-adjusted HR per 10-g/day increase in alcohol intake in women was not statistically significant for primary liver cancer (p for trend = 0.165). We found a nonsignificant increase in risk among nondrinkers as compared to occasional drinkers (multivariate-adjusted HR: 1.50; 95% CI: 0.69, 3.25). Using data from the JACC and JPHC II, the multivariate-adjusted HRs for ex- and never drinkers as compared to occasional drinkers were 3.12 (0.85–11.38) and 1.85 (0.40–8.50), respectively.

In the sensitivity analysis for women, we assumed that one primary liver cancer case occurred in a randomly selected female occasional drinker in the MIYAGI so as to include data from that study. Then we calculated study-specific HRs and conducted the meta-analysis. We repeated this procedure 10 times. The results were essentially unchanged: the point estimates of the pooled multivariate HR of primary liver cancer were 1.43–1.45 for nondrinkers, 0.81–0.82 for an alcohol intake of 0.1–22.9 g/day and 3.72–3.78 for an alcohol intake of 23.0≥g/day.

Table 4 shows the associations of alcohol intake with primary liver cancer risk in men, after stratification by history of liver disease. In the analysis of men without a history of liver disease, the JACC was not included because there were no primary liver cancer cases among occasional drinkers. We found a positive association between alcohol intake and primary liver cancer among men without a history of liver disease (p for trend = 0.010); there was no such association among men with a history of liver disease (p for trend = 0.859). In addition, we found no increased risk among nondrinkers as compared to occasional drinkers in men without a history of liver disease. Among all the pooled multivariate-adjusted models, the p-value for the quadratic term was statistically significant only in women (p = 0.049, Table 3).

Discussion

In this pooled analysis of major population-based cohort studies carried out in Japan, occasional drinkers and those who drank <23.0 g alcohol/day had the lowest risks of primary liver cancer. There was a positive linear association with increasing alcohol intake in drinkers and approximately 70% of the excess risk of primary liver cancer was attributable to participants with an alcohol intake of ≥69.0 g per day. This positive association was pronounced in male drinkers without a history of liver disease; however, no such

Table 4. Pooled multivariate hazard ratios (random effect model) for the association between alcohol intake and liver cancer incidence by history of liver disease in men, 1988–2004

	Nondrinkers	Occasional drinkers (<once/week)	Current drinker, daily alcohol intake (g/day)				Alcohol intake as a continuous variable (per 10 g/day)[1]		
			0.1–22.9	23.0–45.9	46.0–68.9	≥ 69.0	HR	*p* for trend	*p* for heterogeneity
No history of liver disease									
No. of cases	62	17	42	55	37	48			
Multivariate-adjusted HR[2] (95% CI)	1.01 (0.59–1.74)	1.00 (Reference)	0.94 (0.47–1.88)	1.17 (0.68–2.04)	1.16 (0.65–2.07)	1.96 (1.12–3.45)	1.02 (1.01–1.04)	0.010	0.490
History of liver disease									
No. of cases	135	12	31	34	26	27			
Multivariate-adjusted HR[2] (95% CI)	1.54 (0.83–2.84)	1.00 (Reference)	0.73 (0.27–1.96)	0.89 (0.40–2.00)	0.74 (0.30–1.81)	0.80 (0.38–1.67)	1.01 (0.95–1.07)	0.859	0.466

[1]Trend association was assessed after exclusion of nondrinkers. Alcohol intake in occasional drinkers was defined as zero. [2]Multivariate-adjusted HR was adjusted for geographic area (in the JPHC I, JPHC II, and JACC), age (continuous), history of diabetes mellitus (yes, or no), smoking status (never, past, current smoking 1-19 cigarettes/d, and ≥20 cigarettes/d), and coffee intake (almost never, <1 cup/day, ≥1 cup/day). Abbreviations: HR, hazard ratio; CI, confidence interval; JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study.

association was found in men with a history of liver disease. In women, we also found a positive association between alcohol drinking and primary liver cancer risk in current drinkers with an alcohol intake of ≥23.0 g per day.

In addition to the carcinogenicity of acetaldehyde,[31] which is a metabolite of alcohol, several potential biologic mechanisms have been proposed to explain the effect of alcohol on hepatocarcinogenesis, including the induction of cytochrome P-450 2E1, which potentially leads to activation of procarcinogen[32] and inhibition of phase II enzymes, thus affecting the clearance of carcinogens;[33] deficiencies in various anticarcinogenic nutrients,[34] including carotenoids;[35] and aberrant DNA methylation of tumor suppressor genes and oncogenes, which might result from alterations in carbon metabolism due to alcohol intake.[36]

In women, only two prospective studies have conducted dose-specific analyses of alcohol intake and its association with primary liver cancer incidence. In Japan, Goodman et al reported an increased risk of liver cancer in women: the multivariate-adjusted relative risk of women who drank 70 ml of alcohol/week as compared to never drinkers was 2.02 (0.99–4.09).[3] In the United Kingdom, a 1.7-fold risk of liver cancer was found in women who drank ≥15 drinks/week (≥21.4 g alcohol/day) as compared to those who drank ≤2 drinks/week (2.9 g alcohol/day).[6] In our study, we also found a 3.6-fold risk in women who drank ≥23 g alcohol/day as compared to occasional drinkers (<once/week). Because of the limited number of primary liver cancer cases among female drinkers in our study and the use of different alcohol consumption categories in previous studies, it was difficult to assess relative risks among studies. However, the present and previous findings suggest that even moderate alcohol consumption in women increases the risk of primary liver cancer.

We found an increased risk of primary liver cancer in male and female nondrinkers as compared to occasional drinkers. Because the HRs in ex-drinkers are higher than those in never drinkers among both men and women, the increased risk may be due to the former. This explanation is plausible when we consider that ex-drinkers may have stopped drinking due to ill health.

In contrast to the positive association among male drinkers without a history of liver disease, there was no such association in those with a history of liver disease. Although information on liver disease was self-reported and not confirmed by medical records, it is important to consider the possibility that participants changed their drinking behavior. Self-reported information on liver disease indicates awareness of such a condition and suggests recognition of a need to reduce or quit alcohol drinking, as advised by physicians or other health care providers. Because the association among male drinkers with a history of liver disease might be distorted by a reduction in alcohol drinking, the association among participants without liver disease is likely to be a better reflection of the healthy population. The absence of an association in those with a history of liver disease is consistent with findings of

studies conducted among chronic liver disease patients (particularly patients with cirrhosis) that report no association[37,38] or, surprisingly, an inverse association.[39–41]

Our study had several strengths. First, we analyzed data from large scale population-based cohort studies that used validated questionnaires to collect data on alcohol intake. Second, each study controlled for a common set of available variables that are known or believed to cause or prevent primary liver cancer. Third, by pooling data from populations with large variations in alcohol intake, we were able to investigate risk in men with high alcohol intake and to calculate the HR of primary liver cancer in men who drank ≥92.0 g of alcohol/day. Finally, we conducted stratified analysis by history of liver disease, by which we could determine the influence of chronic liver disease on the association between alcohol drinking and primary liver cancer.

The limitations of our study warrant mention. First, we had no information on HBV and HCV infection status. If these viral infections were related to a decrease in alcohol intake, the HRs of primary liver cancer according to alcohol drinking categories would be underestimated. Nonetheless, among healthy participants, including hepatitis virus carriers who were unaware of infection, such a decrease in alcohol intake due to infection is not likely. However, underestimation might occur among participants with chronic liver disease if participants with more severe chronic liver disease tended to drink less alcohol at baseline for any reason (eg, impaired liver function or advice from a physician). Taken together, we cannot exclude the possibility of underestimation of HRs for primary liver cancer in drinkers. A second limitation is that because there were no cases of primary liver cancer among women in the reference category in the MIYAGI, we could not include data from that study in the pooled estimate. Although the number of primary liver cancer cases in the MIYAGI was small (only one and two cases for alcohol intakes of 0.1–22.9 g/day and ≥23.0 g/day, respectively), we conducted a sensitivity analysis and the results were essentially unchanged. Third, we could not obtain information on genetic polymorphisms related to alcohol-metabolizing enzymes. Approximately half of Japanese have a variant allele, aldehyde dehydrogenase 2 (*ALDH2*),[42] which is related to a high blood concentration of acetaldehyde.[43] In a case-control study conducted in Japan, Sakamoto et al suggested that the *ALDH2* polymorphism may modify HCC risk among light to moderate drinkers: the odds ratios of HCC in participants who drank <69 g of alcohol/day, as compared to nondrinkers, were 3.4 (0.9–12.2) in carriers of *ALDH2*2* and 0.8 (0.3–2.2) in noncarriers.[44] The possible interaction between alcohol intake and genetic polymorphisms related to alcohol-metabolizing enzymes on the risk of primary liver cancer requires further study.

In conclusion, this pooled analysis of data from large prospective studies in Japan indicates that avoidance of: (1) heavy alcohol drinking (≥69.0 g alcohol/day) in men and (2) moderate drinking (≥23.0 g alcohol/day) in women may reduce the risk of primary liver cancer.

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Epidemiology

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Association between body mass index and the colorectal cancer risk in Japan: pooled analysis of population-based cohort studies in Japan

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Background: Obesity has been recognized as important risk factors for colorectal cancer. However, limited evidence is available on colorectal cancer and body mass index (BMI) in Asian population.
Methods: We conducted a pooled analysis of eight population-based prospective cohorts studies in Japan with more than 300 000 subjects to evaluate an impact of obesity in terms of BMI on colorectal cancer risk with unified

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categories. We estimated summary hazard ratio (HR) by pooling of study-specific HR for BMI categories with random effect model.

Results: We found a significant positive association between BMI and colorectal cancer risk in male and female. Adjusted HRs for 1 kg/m^2 increase were 1.03 [95% confidence interval (CI) 1.02–1.04] for males and 1.02 (95% CI 1.00–1.03) for females. The association was stronger in colon, especially in proximal colon, relative to rectum. Males showed a stronger association than females. Population attributable fraction for colorectal cancer by BMI ≥25 kg/m^2 was 3.62% (95% CI 1.91–5.30) for males and 2.62% (95% CI 0.74–4.47) for females.

Conclusions: We found significant association between BMI and colorectal cancer risk by pooling of data from cohort studies with considerable number of subjects among Japanese population. This information is important in cancer control planning, especially in Asian population.

Key words: body mass index, cohort study, colorectal cancer, Japanese, obesity, pooled analysis

introduction

A condition of overweight or obese is recognized as one of the strong risk factors on many health conditions including some cancers and more than a billion of people in the world are now in that condition [1]. As in the west, many Asian countries including Japan are experiencing a steep rise in the prevalence of obesity in their populations, although the prevalence remains lower compared with those in the Western countries [2, 3].

A higher body mass index (BMI) has been identified as an independent risk factor for colorectal cancer in many epidemiologic studies [4–11]. Recent meta-analysis including studies mainly from Western countries demonstrated moderate but significant association between BMI and colorectal, especially colon cancer risk [12–14]. Considering different trends in obesity prevalence and colorectal cancer incidence between Western and Asian countries, it is essential to have a concrete estimates of impact of BMI on colorectal cancer incidence in Asian population. A recent pooled analysis from Asian countries reported a positive association between colorectal cancer mortality and BMI [15]; however, to the best of our knowledge, scarce evidence by pooled analysis with considerable population size is available on BMI and colorectal cancer incidence in Asia.

In the present study, we conducted a pooled analysis of eight population-based prospective cohorts studies in Japan with >300 000 subjects to evaluate the impact of high BMI on colorectal cancer risk with unified BMI categories.

materials and methods

study population

The present study was conducted using data from eight representative ongoing large-scale population-based cohort studies in Japan, namely (i) the Japan Public Health Center-based Prospective Study (JPHC-I) [16], (ii) the Japan Public Health Center-based Prospective Study (JPHC-II) [16], (iii) the Japan Collaborative Cohort Study (JACC) [17], (iv) the Miyagi Cohort Study (MIYAGI-I) [18], (v) the Three-Prefecture Cohort Study in Miyagi (MIYAGI-II) [19], (vi) the Three-Prefecture Cohort study in Aichi (AICHI) [19], (vii) the Takayama Study (TAKAYAMA) [20] and (viii) the Ohsaki Cohort Study (OHSAKI) [21]. All of these studies started after the mid-1980s and enrolled >30 000 participants. Furthermore, each included exposure information on anthropometric factors in the baseline questionnaire and collected the incidence or mortality of all cancers as outcome information during follow-up. The relevant institutional ethical review board approved each study. Five of these studies (JPHC-I and -II, JACC, MIYAGI-I and TAKAYAMA) have already published results on the association between BMI and colorectal cancer risk in the respective cohort [8, 20, 22, 23]. In this study, we reanalyzed the results of each study using the updated dataset. Selected characteristics of the cohort studies included in the present study are described in Table 1.

follow-up

Subjects were followed from the baseline survey (JPHC-I and -II: 1990–1994, JACC: 1988, MIYAGI-I: 1990, Miyagi-II: 1984, AICHI: 1958, TAKAYAMA: 1992 and OHSAKI: 1994) until the last date of follow-up in each study (JPHC-I and -II: 2006, JACC: 2001, MIYAGI-I: 2003, MIYAGI-II: 1992, AICHI: 2000, TAKAYAMA: 1999 and OHSAKI: 2003). Residence status in each study, including survival, was confirmed through the residential registry. Information on the cause of death was obtained from death certificates, coded according to the International Classification of Disease, Tenth Revision (ICD-10) [24]. Information on cancer diagnosis was collected for the whole population and was coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) [25].

assessment of outcome

Study outcome was defined as the incidence of colorectal cancer (ICD-O-3 T-code: C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19.9 and C20.9) during the follow-up period of each study. Subjects were categorized for subsite analysis as follows: (i) colorectal cancer overall: C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19.9 and C20.9, (ii) colon cancer: C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8 and C18.9, (iii) proximal colon cancer: C18.0, C18.1, C18.2, C18.3 and C18.4, (iv) distal colon cancer: C18.5, C18.6 and C18.7 and (v) rectal cancer C19.9 and C20.9.

assessment of exposure

BMI was assessed by self-administered questionnaires at baseline in each study. Although the style of the questions differed by study, each study calculated BMI as weight in kilogram divided by square of the height in meter in their questionnaires. BMI was then divided into categories by using identical cut points across studies: <19, 19 to <21, 21 to <23, 23 to <25, 25 to <27, 27 to <30 and ≥30 kg/m^2. We defined 23 to <25 kg/m^2 as reference category. Correlation coefficients that compared BMI estimated from the questionnaire with BMI from actually measured weight and height were JPHC-I and -II: 0.89 in men and 0.90 in women [26] and MIYAGI-I 0.91 for both sexes [5]. Correlation coefficients for height and weight in both sexes in TAKAYAMA were 0.93 and 0.97 [20] and in MIYAGI-I 0.97

Table 1. Characteristics of the eight cohort studies in the pooled analysis of the association between body mass index and colorectal cancer incidence

Study	Population	Age range at baseline, years	Year of baseline survey	Population size	Response rate (%) of the baseline questionnaire	Method of follow-up	For the present pooled analysis							
							Age range, years	Last follow-up time	Mean follow-up period, years	Outcome	Size of the cohort		Number of cancer cases	
											Men	Women	Men	Women
JPHC-I	Japanese residents of 5 public health center areas in Japan	40–59	1990	61 595	82	Cancer registry and death certificate	40–59	2006	16.1	Incidence	20 191	21 686	546	320
JPHC-II	Japanese residents of 6 public health center areas in Japan	40–69	1993–1994	78 825	80	Cancer registry and death certificate	40–69	2006	12.8	Incidence	28 928	32 015	619	370
JACC	Residents from 45 areas throughout Japan	40–79	1988–1990	110 792	83	Cancer registry (selected areas: 22) and death certificate	40–79	2001	10.3	Incidence	24 513	35 483	487	345
MIYAGI-I	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47 605	92	Cancer registry and death certificate	40–64	2003	12.7	Incidence	21 109	22 685	420	270
MIYAGI-II	Residents of 3 municipalities in Miyagi Prefecture, Japan	40+	1984	31 345	94	Cancer registry and death certificate	40+	1992	7.6	Incidence	13 010	15 944	164	122
AICHI	Residents of 2 municipalities in Aichi Prefecture, Japan	40–103	1985	33 529	90	Cancer registry and death certificate	40–103	2000	11.5	Incidence	15 253	16 895	196	146
TAKAYAMA	Residents of Takayama city, Gifu Prefecture, Japan	35+	1992	31 552	85	Colonoscopy data at two main hospitals	35+	1999	6.9	Incidence	13 392	15 537	149	113
OHSAKI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–79	1994	52 029	95	Cancer registry and death certificate	40–79	2003	7.7	Incidence	21 531	23 212	474	238
Total				447 272							157 927	183 457	3055	1924

JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study; AICHI, Aichi Cohort Study; OHSAKI, Ohsaki Cohort Study.

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and 0.85 [5], respectively. JACC and OHSAKI, for which information on the validation of BMI was not available, utilized the same questions on weight and height as MIYAGI-I. For MIYAGI-II and AICHI, there has been no information on the validation of BMI; the question was similar to JPHC-I and -II.

statistical analysis

Person-years of follow-up were calculated from the date of baseline survey in each study until the date of diagnosis of any cancer. To be pooled in estimation of summary statistics, we conducted study-specific analysis. Each analysis was stratified by sex. For females, we further stratified the analysis by menopausal status. Each analysis used a Cox proportional hazards model to estimate the hazard ratios (HR) and their two-sided 95% confidence intervals (CI) of colorectal cancer by each BMI category. All studies carried out two models in the estimation of HRs, model 1: age (and area within each study for JPHC and JACC)-adjusted HRs and model 2: smoking and drinking in addition to model 1. In model 2, smoking for male was categorized into never smoker, former smoker, current smoker with <20 cigarettes/day, current smoker with ≥20 pieces/day or missing and that for female was categorized into never smoker, former smoker, current smoker and missing. Drinking for male was categorized into nondrinker, occasional drinker (less than once a week) and current drinker (<23, 23 to <46, 46 to <69, 69 to <92 and ≥92 ethanol g/day) and that for female was nondrinker, occasional drinker and current drinker (<23 and ≥23 ethanol g/day). For six of the eight cohort studies, we adjusted other potential confounders (model 3). Model 3 included total energy (kilocalories per day), red meat (grams per day), dietary fiber (grams per day), calcium (milligrams per day), folate (micrograms per day) consumption in quartile in each study and recreational physical activity (JPHC-I and -II: almost everyday or not and JACC, MIYAGI-I and OHSAKI: ≥5 h/day or not). All the analyses were done by SAS (Version 9.1; SAS Institute, Inc., Cary, NC) or STATA (Version 10.1; Stata Corporation, College Station, TX) statistical software was used for estimations.

To obtain a single pooled estimate of the HR from the individual studies for each category, we applied a random effects model [27]. We did not include in the study any pooled estimates for categories without cases. The extent of heterogeneity for each category was indicated by Cochran's Q-statistic, which was considered statistically significant when $P < 0.10$. The I^2-statistic was also reported to describe the percentage of total variation in the study-specific HRs, which was due to heterogeneity [28]. Dose–response relationship was examined by models in which actual BMI values were included as explanatory variable, which would provide HRs by 1 kg/m^2 increase of BMI. The 'metan' command (http://www.stata.com/stb/stb44) for STATA was used for meta-analysis.

In addition, to express the impact of BMI on the risk of colorectal cancer, the population attributable fraction (PAF) (%) was estimated as pd(HR−1)/HR, where pd is the proportion of cases exposed to the risk factors [29].

results

As shown in Table 1, the present pooled analysis included eight large-scale population-based prospective cohort studies comprising 341 384 subjects (157 927 males and 183 457 females) with 4979 incident colorectal cancer cases (3055 males and 1924 females) during 3 765 498 person-years of follow-up (average follow-up: 11.0 years). At baseline, those with BMI ≥25 kg/m^2 consisted 23.3% for males and 25.2% for females. These values are comparable to those reported in the same period with the same age group [2].

Table 2 shows results for male. For colorectal cancer, we observed statically significant HRs over unity for those with BMI 27–29.9 [age, area, smoking and drinking adjusted (model 2) HR (aHR) = 1.21, 95% CI 1.05–1.40] and for those with BMI ≥30 (aHR = 1.50, 95% CI 1.15–1.96). Moreover, it showed linear trend (aHR for per 1 kg/m^2 increase in BMI = 1.03, 95% CI 1.02–1.04). Similar trends were seen in other patterns of analyses for colorectal cancer. Those with BMI <25 showed aHR below unity, though they were not statistically significant. In subsite-specific analyses, we observed a consistent result in terms of linear trends except rectal cancer. For rectal cancer, only those with BMI ≥30 kg/m^2 showed significant association. Interestingly, effect of higher BMI appeared in smaller BMI values in more proximal site. Proximity of subsites seemed associated with smaller threshold of BMI. A significant association with proximal colon cancer appeared in those with BMI >25 kg/m^2, while the significant association appeared in BMI >27 kg/m^2 for distal colon cancer and BMI ≥30 kg/m^2 for rectal cancer. Significant reduced risk was not observed in leaner subgroups using overall dataset. We also evaluated potential heterogeneity of results. We found that colorectal cancer analyses showed marginally significant heterogeneity, but for subsite-specific analyses, there seemed no significant heterogeneity across studies.

Table 3 shows results for females. Although point estimates of aHRs were relatively smaller than those for males, trends of association were consistent with males. The aHRs for colorectal cancer by BMI per 1 kg/m^2 were 1.02 (95% CI 1.00–1.03). In the subsite-specific analyses, colon cancer showed positive association regardless of subsite. In contrast, rectal cancer did not show linear association at all. In distal colon cancer, significant association was seen for those with BMI 25–26.9 kg/m^2 group and ≥30 kg/m^2 groups but not with 27–29.9 kg/m^2 groups. Stratified analysis by menopausal status showed that the association was significant in colon cancers among postmenopausal women but not in premenopausal women. For rectal cancer, aHRs higher than unity were seen in those with BMI <19 kg/m^2 though not significant. We did not see any statistically significant heterogeneity in all patterns of analysis.

We observed statistically significant association between higher BMI and colorectal cancer risk in this pooled analysis. By using current results, we estimated PAF of BMI ≥25 kg/m^2 on colorectal cancer in men and women. For males, PAFs estimates were 1.56% for BMI 25–26.9 group, 1.42% for 27–29.9 group and 0.64% for 30 or higher group. As a whole, 3.62% (95% CI 1.91–5.30) was attributed to 25 or higher BMI for male colorectal cancer. For females, PAFs estimates were 0.89% for BMI 25–26.9 group, 0.91% for 27–29.9 group, 0.83% for 30 or higher group and 2.62% (95% CI 0.74–4.47) for a whole.

discussion

This study is the first and the largest pooled analysis examining an association between BMI and colorectal cancer risk among Asian population, to the best of our knowledge. By pooling data of eight population-based cohort studies with

Table 2. Pooled analysis for body mass index (BMI) and colorectal cancer risk according to subsite[d] (male)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m^2	19 to <21 kg/m^2	<23 kg/m^2	23 to <25 kg/m^2	25 to <27 kg/m^2	27 to <30 kg/m^2	30 kg/m^2	Trend (per 1 kg/m^2)	Trend *P*	*P*, I^2 (%) For trend	For the highest category
Number of subjects (*n* =)	9512	27 136	42 789	41 648	22 875	11 436	2531				
Person-years (*n* =)	90 944.5	286 483.52	464 961.22	463 999.5	257 394.43	130 096.7	28 723.75				
Colorectal cancer											
Number of cases (*n* =)	159	501	801	805	480	250	59				
CR (per 100 000)	174.83	174.88	172.27	173.49	186.48	192.16	205.4				
HR (model 1) overall[a]	0.86 (0.72–1.02)	0.95 (0.85–1.06)	0.95 (0.86–1.05)	Reference	1.107 (0.99–1.24)	**1.20 (1.04–1.38)**	**1.47 (1.13–1.93)**	**1.03 (1.02–1.04)**	<0.001	*P* = 0.554, 0	*P* = 0.056, 51.2
HR (model 2) overall[b]	0.87 (0.73–1.03)	0.94 (0.84–1.05)	0.94 (0.86–1.04)	Reference	1.11 (0.99–1.24)	**1.21 (1.05–1.40)**	**1.50 (1.15–1.96)**	**1.03 (1.02–1.04)**	<0.001	*P* = 0.462, 0	*P* = 0.061, 50.2
HR (model 3) overall[c]	0.91 (0.74–1.12)	0.99 (0.88–1.12)	0.95 (0.85–1.06)	Reference	**1.14 (1.01–1.29)**	**1.24 (1.06–1.44)**	**1.24 (1.06–1.44)**	**1.03 (1.02–1.04)**	<0.001	*P* = 0.643, 0	***P* = 0.010, 69.8**
HR (model 1) excluding early cases[a]	**0.80 (0.66–0.98)**	0.95 (0.83–1.07)	0.93 (0.84–1.04)	Reference	**1.13 (1.00–1.28)**	**1.22 (1.04–1.43)**	**1.57 (1.18–2.09)**	**1.04 (1.02–1.05)**	<0.001	*P* = 0.637, 0	*P* = 0.190, 31.2
HR (model 2) excluding early cases[b]	**0.81 (0.66–0.99)**	0.93 (0.82–1.05)	0.93 (0.83–1.03)	Reference	**1.13 (1.00–1.28)**	**1.23 (1.05–1.45)**	**1.59 (1.20–1.35)**	**1.04 (1.03–1.05)**	<0.001	*P* = 0.652, 0	*P* = 0.219, 27.5
HR (model 3) excluding early cases[c]	0.86 (0.68–1.09)	0.99 (0.86–1.14)	0.93 (0.83–1.05)	Reference	**1.16 (1.02–1.33)**	**1.26 (1.06–1.49)**	**1.58 (1.15–2.17)**	**1.04 (1.02–1.05)**	<0.001	*P* = 0.952, 0	*P* = 0.042, 59.5
Colon cancer											
Number of cases (*n* =)	98	317	473	512	319	168	32				
CR (per 100 000)	107.76	110.65	101.73	110.34	123.93	129.13	111.41				
HR (model 1) overall[a]	0.82 (0.66–1.03)	0.94 (0.82–1.08)	0.88 (0.77–1.00)	Reference	**1.16 (1.01–1.34)**	**1.28 (1.07–1.52)**	1.38 (0.96–1.98)	**1.04 (1.02–1.06)**	<0.001	*P* = 0.183, 16.9	*P* = 0.183, 32.1
HR (model 2) overall[b]	0.84 (0.67–1.04)	0.94 (0.81–1.08)	**0.86 (0.76–0.97)**	Reference	**1.16 (1.01–1.34)**	**1.27 (1.07–1.52)**	1.37 (0.96–1.98)	**1.04 (1.02–1.06)**	<0.001	*P* = 0.300, 16.5	*P* = 0.213, 28.2
HR (model 3) overall[c]	0.91 (0.70–1.17)	1.00 (0.85–1.16)	0.87 (0.75–1.00)	Reference	**1.17 (1.01–1.36)**	**1.31 (1.09–1.58)**	1.47 (0.99–2.18)	**1.04 (1.02–1.06)**	<0.001	*P* = 0.358, 9.1	*P* = 0.096, 52.7
HR (model 1) excluding early cases[a]	**0.76 (0.59–0.99)**	0.98 (0.84–1.14)	0.90 (0.77–1.02)	Reference	**1.18 (1.01–1.38)**	**1.32 (1.09–1.60)**	**1.67 (1.15–2.44)**	**1.05 (1.03–1.06)**	<0.001	*P* = 0.500, 0	*P* = 0.487, 0

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Table 2. (*Continued*)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m^2	19 to <21 kg/m^2	<23 kg/m^2	23 to <25 kg/m^2	25 to <27 kg/m^2	27 to <30 kg/m^2	30 kg/m^2	Trend (per 1 kg/m^2)	Trend *P*	*P*, I^2 (%) For trend	For the highest category
HR (model 2) excluding early cases[b]	0.77 (0.59–1.00)	0.97 (0.83–1.13)	0.88 (0.77–1.02)	Reference	**1.18 (1.01–1.38)**	**1.32 (1.09–1.60)**	**1.66 (1.14–2.43)**	**1.05 (1.03–1.07)**	<0.001	*P* = 0.489, 0	*P* = 0.551, 0
HR (model 3) excluding early cases[c]	0.81 (0.60–1.11)	1.04 (0.87–1.23)	0.88 (0.75–1.02)	Reference	**1.18 (1.00–1.39)**	**1.34 (1.09–1.65)**	**1.81 (1.20–2.72)**	**1.04 (1.02–1.06)**	<0.001	*P* = 0.556, 0	*P* = 0.411, 0
Proximal colon cancer[d]											
Number of cases (*n* =)	34	114	177	182	126	66	11				
CR (per 100 000)	37.39	39.79	38.07	39.22	48.95	50.73	38.3				
HR (model 1) overall[a]	0.94 (0.64–1.37)	0.98 (0.77–1.25)	0.95 (0.77–1.17)	Reference	**1.29 (1.03–1.60)**	**1.43 (1.07–1.91)**	1.57 (0.84–2.92)	1.01 (1.00–1.01)	0.053	*P* = 0.794, 0	*P* = 0.891, 0
HR (model 2) overall[b]	0.98 (0.67–1.44)	1.01 (0.79–1.28)	0.96 (0.78–1.18)	Reference	**1.29 (1.02–1.62)**	**1.42 (1.06–1.89)**	1.55 (0.83–2.88)	**1.04 (1.01–1.06)**	0.011	*P* = 0.639, 0	*P* = 0.931, 0
HR (model 3) overall[c]	0.98 (0.64–1.51)	1.08 (0.84–1.40)	0.96 (0.76–1.20)	Reference	1.21 (0.95–1.56)	**1.39 (1.02–1.90)**	1.61 (0.83–3.09)	1.03 (1.00–1.06)	0.09	*P* = 0.909, 0	*P* = 0.761, 0
HR (model 1) excluding early cases[a]	0.83 (0.53–1.30)	1.00 (0.78–1.30)	0.90 (0.72–1.13)	Reference	**1.31 (1.03–1.67)**	**1.47 (1.08–1.98)**	1.65 (0.86–3.17)	**1.05 (1.02–1.08)**	0.001	*P* = 0.706, 0	*P* = 0.785, 0
HR (model 2) excluding early cases[b]	0.87 (0.55–1.36)	1.02 (0.78–1.32)	0.91 (0.73–1.15)	Reference	**1.30 (1.02–1.66)**	**1.45 (1.07–1.97)**	1.63 (0.85–3.13)	**1.05 (1.02–1.08)**	0.002	*P* = 0.656, 0	*P* = 0.839, 0
HR (model 3) excluding early cases[c]	0.84 (0.50–1.41)	1.08 (0.82–1.44)	0.92 (0.72–1.18)	Reference	1.23 (0.94–1.60)	**1.40 (1.01–1.95)**	1.68 (0.84–3.37)	**1.04 (1.01–1.07)**	0.02	*P* = 0.695, 0	*P* = 0.621, 0
Distal colon cancer[d]											
Number of cases (*n* =)	46	155	232	252	160	82	19				
CR (per 100 000)	50.58	54.1	49.9	54.31	62.16	63.03	66.15				
HR (model 1) overall[a]	0.91 (0.66–1.26)	0.97 (0.79–1.18)	0.88 (0.73–1.05)	Reference	1.18 (0.97–1.45)	1.27 (0.99–1.63)	**1.77 (1.10–2.87)**	1.00 (1.00–1.01)	0.776	***P* = 0.002, 69.5**	*P* = 0.262, 22.8
HR (model 2) overall[b]	0.92 (0.66–1.28)	0.95 (0.77–1.16)	0.87 (0.73–1.04)	Reference	1.19 (0.97–1.45)	**1.28 (1.00–1.65)**	**1.80 (1.11–2.92)**	**1.05 (1.03–1.08)**	<0.001	***P* < 0.001, 100**	*P* = 0.293, 18.6
HR (model 3) overall[c]	1.01 (0.70–1.46)	0.94 (0.76–1.18)	0.83 (0.68–1.01)	Reference	1.20 (0.97–1.48)	**1.33 (1.02–1.73)**	**1.77 (1.06–3.00)**	**1.05 (1.03–1.08)**	<0.001	*P* = 0.627, 0	*P* = 0.126, 47.5

Table 2. (*Continued*)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m^2	19 to <21 kg/m^2	<23 kg/m^2	23 to <25 kg/m^2	25 to <27 kg/m^2	27 to <30 kg/m^2	30 kg/m^2	Trend (per 1 kg/m^2)	Trend *P*	*P*, I^2 (%) For trend	For the highest category
HR (model 1) excluding early cases[a]	0.89 (0.62–1.29)	1.01 (0.81–1.26)	0.93 (0.77–1.14)	Reference	1.21 (0.97–1.51)	**1.37 (1.05–1.80)**	**2.20(1.35–3.66)**	**1.05 (1.03–1.08)**	<0.001	*P* = 0.584, 0	*P* = 0.443, 0
HR (model 2) excluding early cases[b]	0.90 (0.62–1.30)	0.99 (0.80–1.24)	0.92 (0.76–1.12)	Reference	1.21 (0.97–1.51)	**1.38 (1.05–1.82)**	**2.24 (1.35–3.69)**	**1.05 (1.03–1.08)**	<0.001	*P* = 0.598, 0	*P* = 0.445, 0
HR (model 3) excluding early cases[c]	1.00 (0.67–1.52)	1.00 (0.79–1.28)	0.87 (0.70–1.08)	Reference	1.22 (0.97–1.55)	**1.44 (1.08–1.91)**	**2.24 (1.31–3.82)**	**1.06 (1.03–1.08)**	<0.001	*P* = 0.728, 0	*P* = 0.174, 42.8
Rectal cancer											
Number of cases (*n* =)	59	179	325	284	158	80	26				
CR (per 100 000)	64.87	62.48	69.9	61.21	61.38	61.49	90.52				
HR (model 1) overall[a]	0.93 (0.70–1.24)	0.97 (0.80–1.17)	1.10 (0.94–1.29)	Reference	1.03 (0.85–1.25)	1.16 (0.89–1.49)	**1.79 (1.19–2.69)**	1.02 (1.00–1.04)	0.142	*P* = 0.979, 0	*P* = 0.467, 0
HR (model 2) overall[b]	0.92 (0.69–1.23)	0.95 (0.79–1.15)	1.09 (90.93–1.28)	Reference	1.04 (0.86–1.27)	1.17 (0.91–1.52)	**1.85 (1.23–2.78)**	1.02 (1.00–1.04)	0.102	*P* = 0.980, 0	*P* = 0.450, 0
HR (model 3) overall[c]	0.91 (0.65–1.27)	0.98 (0.80–1.21)	1.12 (0.94–1.33)	Reference	1.12 (0.91–1.37)	1.20 (0.91–1.58)	1.57 (0.97–2.53)	1.02 (0.99–1.04)	0.202	*P* = 0.924, 0	*P* = 0.256, 24.9
HR (model 1) excluding early cases[a]	0.96 (0.69–1.32)	0.88 (0.71–1.10)	1.03 (0.86–1.23)	Reference	1.05 (0.85–1.30)	1.19 (0.89–1.58)	**1.87 (1.21–2.88)**	**1.03 (1.00–1.05)**	0.035	*P* = 0.582, 0	*P* = 0.701, 0
HR (model 2) excluding early cases[b]	0.95 (0.69–1.31)	0.86 (0.70–1.07)	1.01 (0.85–1.21)	Reference	1.06 (0.86–1.32)	1.21 (0.90–1.61)	**1.92 (1.25–2.97)**	**1.03 (1.00–1.05)**	0.023	*P* = 0.517, 0	*P* = 0.688, 0
HR (model 3) excluding early cases[c]	0.97 (0.67–1.41)	0.89 (0.70–1.14)	1.03 (0.84–1.26)	Reference	1.13 (90.90–1.42)	1.20 (0.88–1.65)	1.52 (0.91–2.55)	**1.03 (1.00–1.05)**	0.069	*P* = 0.504, 0	*P* = 0.721, 0

[a]Adjusted for age and area.

[b]Adjusted for age, area, smoking (never, former, current <20 pieces/day, current ≥20 pieces/day or unknown) and drinking (never, <1 week/day, current <23 g/day, 23 to <46 g/day, 46 to <69, 69 to <92 and ≥92 g/day).

[c]Adjusted for age, area, smoking (never, former, current <20 pieces/day, current ≥20 pieces/day or unknown), drinking (never, <1 week/day, current <23 g/day, 23 to <46 g/day, 46 to <69, 69 to <92 and ≥92 g/day) and total energy, red meat in quartile, dietary fiber in quartile, calcium intake in quartile, folate intake in quartile and recreational physical exercise. This model is only for JPHC1, JPHC2, JACC, MIYAGI1, OHSAKI and Takayama based on availability of adjusting factors.

[d]Those whose ICD-O-3 topology code was C18.8 were excluded from analysis.

BMI, body mass index; HR, hazard ratio; CI, confidence interval; JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study; AICHI, Aichi Cohort Study; OHSAKI, Ohsaki Cohort Study; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; CR, crude risk.

HRs values in bold show statistical significance.

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Table 3. Pooled analysis for BMI and colorectal cancer risk according to subsite[d] (female)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m^2	19 to <21 kg/m^2	<23 kg/m^2	23 to <25 kg/m^2	25 to <27 kg/m^2	27 to <30 kg/m^2	30 kg/m^2	Trend (per 1 kg/m^2)	Trend *P*	P_h, I^2 (%) For trend	For the highest category
Number of subjects (*n* =)	14 467	32 423	48 060	42 249	25 623	15 830	4805				
Person-years (*n* =)	146 751.95	353 214.1	537 047.03	478 890.4	291 734.7	180 691.72	54 564.75				
Colorectal cancer											
Number of cases (*n* =)	130	314	480	438	301	192	69				
CR (per 100 000)	88.58	88.9	89.38	91.46	103.18	106.26	126.46				
HR1 overall[a]	0.93 (0.76–1.14)	1.00 (0.86–1.16)	1.00 (0.88–1.14)	Reference	1.08 (0.93–1.25)	1.10 (0.93–1.31)	**1.31 (1.01–1.69)**	**1.02 (1.01–1.04)**	0.002	*P* = 0.387, 5.7	*P* = 0.894, 0
HR2 overall[b]	0.93 (0.76–1.13)	1.00 (0.86–1.16)	1.00 (0.88–1.14)	Reference	1.06 (0.92–1.23)	1.10 (0.93–1.31)	**1.30 (1.00–1.68)**	**1.02 (1.00–1.03)**	0.032	*P* = 0.505, 0	*P* = 0.870, 0
HR3 overall[c]	0.91 (0.73–1.15)	0.95 (0.80–1.13)	1.01 (0.88–1.17)	Reference	1.07 (0.91–1.25)	1.06 (0.88–1.28)	1.17 (0.87–1.57)	**1.07 (1.05–1.08)**	<0.001	***P* < 0.001, 97.9**	*P* = 0.854, 0
HR1 excluding early cases[a]	0.94 (0.74–1.18)	1.04 (0.88–1.22)	1.01 (0.87–1.17)	Reference	**1.19 (1.01–1.40)**	**1.22 (1.01–1.47)**	1.23 (0.91–1.66)	**1.02 (1.01–1.04)**	0.007	*P* = 0.909, 0	*P* = 0.941, 0
HR2 excluding early cases[b]	0.93 (0.74–1.18)	1.03 (0.87–1.21)	1.01 (0.87–1.17)	Reference	**1.18 (1.00–1.38)**	**1.21 (1.00–1.47)**	1.21 (0.90–1.64)	**1.02 (1.00–1.04)**	0.015	*P* = 0.749, 0	*P* = 0.935, 0
HR3 excluding early cases[c]	0.98 (0.75–1.27)	0.97 (0.81–1.18)	1.00 (0.85–1.17)	Reference	1.17 (0.98–1.40)	1.16 (0.94–1.42)	1.12 (0.81–1.57)	**1.02 (1.00–1.03)**	0.101	*P* = 0.786, 0	*P* = 0.874, 0
Colon cancer											
Number of cases (*n* =)	76	215	330	512	217	136	48				
CR (per 100 000)	51.79	60.87	61.45	106.91	74.38	75.27	87.97				
HR1 overall[a]	0.80 (0.62–1.04)	1.00 (0.83–1.20)	1.03 (0.88–1.21)	Reference	**1.19 (1.00–1.43)**	1.22 (0.99–1.50)	**1.40 (1.03–1.91)**	**1.04 (1.02–1.06)**	<0.001	***P* = 0.018, 58.6**	*P* = 0.902, 0
HR2 overall[b]	0.80 (0.61–1.04)	1.00 (0.83–1.20)	1.03 (0.88–1.21)	Reference	1.18 (0.99–1.41)	1.22 (0.99–1.51)	**1.39 (1.02–1.90)**	**1.04 (1.03–1.06)**	<0.001	***P* = 0.002, 69.4**	*P* = 0.862, 0
HR3 overall[c]	0.71 (0.52–0.97)	0.87 (0.71–1.07)	1.00 (0.84–1.19)	Reference	**1.21 (1.02–1.44)**	1.11 (0.88–1.39)	1.18 (0.83–1.68)	**1.03 (1.01–1.05)**	0.003	*P* = 0.833, 0	*P* = 0.984, 0
HR1 excluding early cases[a]	0.83 (0.62–1.12)	1.00 (0.80–1.22)	1.03 (0.86–1.23)	Reference	**1.27 (1.04–1.54)**	**1.29 (1.03–1.61)**	**1.47 (1.05–2.06)**	**1.04 (1.02–1.06)**	<0.001	*P* = 0.753, 0	*P* = 0.933, 0

Table 3. (*Continued*)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m^2	19 to <21 kg/m^2	<23 kg/m^2	23 to <25 kg/m^2	25 to <27 kg/m^2	27 to <30 kg/m^2	30 kg/m^2	Trend (per 1 kg/m^2)	Trend *P*	*P*, I^2 (%) For trend	For the highest category
HR2 excluding early cases[b]	0.83 (0.62–1.12)	0.99 (0.80–1.21)	1.02 (0.86–1.22)	Reference	**1.25 (1.03–1.52)**	**1.29 (1.03–1.61)**	**1.46 (1.04–2.04)**	**1.04 (1.02–1.06)**	<0.001	*P* = 0.757, 0	*P* = 0.907, 0
HR3 excluding early cases[c]	0.83 (0.59–1.16)	0.86 (0.68–1.09)	0.98 (0.80–1.19)	Reference	**1.24 (1.00–1.53)**	1.19 (0.93–1.53)	1.31 (0.89–1.91)	**1.04 (1.02–1.06)**	0.001	*P* = 0.687, 0	*P* = 0.858, 0
Proximal colon cancer											
Number of cases (*n* =)	33	103	176	182	107	84	25				
CR (per 100 000)	22.49	29.16	32.77	38	36.68	46.49	45.82				
HR1 overall[a]	0.76 (0.51–1.13)	0.98 (0.76–1.27)	1.07 (0.86–1.33)	Reference	1.09 (0.84–1.40)	**1.34 (1.02–1.77)**	1.40 (0.92–2.15)	**1.04 (1.01–1.06)**	0.002	*P* = 0.788, 0	*P* = 0.596, 0
HR2 overall[b]	0.77 (0.52–1.14)	0.99 (0.76–1.28)	1.07 (0.86–1.33)	Reference	1.06 (0.82–1.38)	**1.35 (1.02–1.77)**	1.38 (0.89–2.13)	**1.04 (1.01–1.06)**	0.002	*P* = 0.771, 0	*P* = 0.548, 0
HR3 overall[c]	0.67 (0.43–1.05)	0.85 (0.64–1.13)	1.04 (0.83–1.31)	Reference	1.01 (0.77–1.32)	1.20 (0.90–1.61)	1.26 (0.79–1.99)	**1.03 (1.01–1.06)**	0.009	*P* = 0.757, 0	*P* = 0.633, 0
HR1 excluding early cases[a]	0.81 (0.53–1.25)	0.95 (0.71–1.26)	0.99 (0.78–1.26)	Reference	1.13 (0.87–1.48)	**1.36 (1.02–1.83)**	1.56 (0.99–2.43)	**1.05 (1.02–1.07)**	<0.001	*P* = 0.641, 0	*P* = 0.460, 0
HR2 excluding early cases[b]	0.82 (0.53–1.26)	0.95 (0.71–1.26)	0.99 (0.78–1.26)	Reference	1.11 (0.85–1.46)	**1.36 (1.02–1.83)**	1.52 (0.96–2.40)	**1.05 (1.02–1.07)**	<0.001	*P* = 0.629, 0	*P* = 0.406, 3.1
HR3 excluding early cases[c]	0.79 (0.50–1.27)	0.82 (0.60–1.11)	0.95 (0.74–1.23)	Reference	1.06 (0.80–1.42)	1.25 (0.92–1.72)	1.38 (0.85–2.26)	**1.04 (1.02–1.07)**	0.002	*P* = 0.636, 0	*P* = 0.394, 3.5
Distal colon cancer											
Number of cases (*n* =)	23	84	115	252	76	40	19				
CR (per 100 000)	15.67	23.78	21.41	52.62	26.05	22.14	34.82				
HR1 overall[a]	0.73 (0.46–1.17)	1.09 (0.80–1.47)	1.01 (0.77–1.33)	Reference	1.24 (0.91–1.69)	1.08 (0.74–1.58)	1.76 (1.06–2.92)	1.03 (1.00–1.06)	0.071	*P* = 0.643, 0	*P* = 0.847, 0
HR2 overall[b]	0.72 (0.45–1.15)	1.08 (0.80–1.46)	1.00 (0.76–1.31)	Reference	1.24 (0.91–1.69)	1.07 (0.74–1.56)	1.76 (1.06–2.91)	1.03 (1.00–1.06)	0.063	*P* = 0.659, 0	*P* = 0.853, 0
HR3 overall[c]	0.78 (0.46–1.31)	1.03 (0.73–1.44)	0.98 (0.72–1.32)	Reference	1.31 (0.93–1.84)	1.08 (0.71–1.65)	1.42 (0.76–2.66)	1.02 (0.99–1.05)	0.258	*P* = 0.630, 0	*P* = 0.745, 0

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Table 3. (*Continued*)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m^2	19 to <21 kg/m^2	<23 kg/m^2	23 to <25 kg/m^2	25 to <27 kg/m^2	27 to <30 kg/m^2	30 kg/m^2	Trend (per 1 kg/m^2)	Trend *P*	*P*, I^2 (%) For trend	For the highest category
HR1 excluding early cases[a]	0.94 (0.56–1.59)	1.11 (0.78–1.58)	1.07 (0.79–1.46)	Reference	**1.47 (1.05–2.07)**	1.28 (0.85–1.92)	**1.84 (1.03–3.27)**	1.03 (1.00–1.06)	0.062	*P* = 0.337, 11.9	*P* = 0.718, 0
HR2 excluding early cases[b]	0.93 (0.55–1.57)	1.10 (0.77–1.57)	1.06 (0.78–1.44)	Reference	**1.47 (1.05–2.06)**	1.28 (0.85–1.92)	**1.85 (1.04–3.28)**	1.03 (1.00–1.07)	0.053	*P* = 0.360, 9.1	*P* = 0.760, 0
HR3 excluding early cases[c]	1.05 (0.58–1.91)	1.04 (0.69–1.56)	1.03 (0.73–1.46)	Reference	**1.62 (1.12–2.35)**	1.28 (0.80–2.06)	1.85 (0.91–3.78)	**1.04 (1.01–1.08)**	0.011	*P* = 0.112, 44.0	*P* = 0.472, 0
Rectal cancer											
Number of cases (*n* =)	53	97	147	284	80	54	20				
CR (per 100 000)	36.12	27.46	27.37	59.3	27.42	29.89	36.65				
HR1 overall[a]	1.31 (0.95–1.80)	0.99 (0.76–1.29)	0.94 (0.75–1.18)	Reference	0.89 (0.67–1.18)	0.93 (0.68–1.28)	1.35 (0.83–2.18)	1.00 (0.98–1.03)	0.946	*P* = 0.677, 0	*P* = 0.472, 0
HR2 overall[b]	1.31 (0.95–1.81)	0.98 (0.76–1.27)	0.94 (0.74–1.18)	Reference	0.88 (0.66–1.17)	0.92 (0.67–1.27)	1.33 (0.82–2.15)	1.00 (0.99–1.00)	0.158	*P* = 0.894, 0	*P* = 0.478, 0
HR3 overall[c]	1.44 (0.99–2.08)	1.12 (0.84–1.50)	1.05 (0.81–1.35)	Reference	0.88 (0.64–1.20)	0.99 (0.70–1.39)	1.39 (0.81–2.39)	1.00 (0.97–1.03)	0.785	*P* = 0.293, 18.5	*P* = 0.397, 0
HR1 excluding early cases[a]	1.35 (0.93–1.96)	1.07 (0.80–1.42)	0.94 (0.72–1.22)	Reference	1.04 (0.76–1.42)	1.05 (0.74–1.49)	1.13 (0.62–2.04)	0.98 (0.95–1.01)	0.23	*P* = 0.882, 0	*P* = 0.625, 0
HR2 excluding early cases[b]	1.35 (0.93–1.97)	1.06 (0.80–1.42)	0.94 (0.72–1.22)	Reference	1.03 (0.75–1.40)	1.04 (0.73–1.48)	1.11 (0.61–2.01)	0.98 (0.95–1.01)	0.203	*P* = 0.876, 0	*P* = 0.623, 0
HR3 excluding early cases[c]	1.52 (0.99–2.34)	1.23 (0.89–1.70)	1.05 (0.78–1.40)	Reference	1.00 (0.71–1.41)	1.13 (0.77–1.67)	1.02 (0.50–2.06)	**0.97 (0.94–1.00)**	0.048	*P* = 0.984, 0	*P* = 0.562, 0

[a]Adjusted for age and area.

[b]Adjusted for age, area, smoking (never, former, current or unknown) and drinking (never, <1 week/day, current <23 g/day, ≥23 g/day).

[c]Adjusted for age, area, smoking (never, former, current or unknown), drinking (never, <1 week/day, current <23 g/day, ≥23 g/day) and total energy, red meat in quartile, dietary fiber in quartile, calcium intake in quartile, folate intake in quartile and recreational physical exercise. This model is only for JPHC1, JPHC2, JACC, MIYAGI1, OHSAKI and Takayama based on availability of adjusting factors.

[d]Those whose ICD-O-3 topology code was C18.8 were excluded from analysis.

BMI, body mass index; HR, hazard ratio; CI, confidence interval; JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study; AICHI, Aichi Cohort Study; OHSAKI, Ohsaki Cohort Study; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; CR, crude risk.

>300 000 Japanese, we have demonstrated that higher BMI increases the risk of colorectal cancer in Japan. The association was stronger in males than in females and the pattern of association between BMI and risk were stronger in colon than in rectum. Our finding is consistent with the former meta-analysis using studies mainly from Western countries [12–14]. A recent meta-analysis of 58 studies showed that HRs for colorectal cancer by 5 kg/m^2 BMI increase in Western populations (1.23 for North American population and 1.13 in European population) [14]. This is almost comparable with our finding in this pooled analysis (1.16 for 5 kg/m^2 increase). In terms of sex difference, the study showed HRs for BMI ≥30 kg/m^2 as 1.53 for men and 1.26 for females [14] and these were similar in our analysis (Tables 1 and 2). Similarly, a heterogeneity by subsite is comparable between ours and the published meta-analyses.

To date, only a limited numbers of prospective studies in Japan have been conducted to evaluate association between colorectal cancer and BMI [8, 20, 22, 23]. One reported significant positive association only in colon cancer in women [22], another reported significant association with colorectal cancer in women [23], while the rest reported positive association in colorectal and colon cancer in men [8, 20]. The reason for this heterogeneity might partly be due to limited statistical power to detect the association in each study. In this sense, an approach of this study might resolve statistical limitations in each of individual study result of this study is very important in terms of having stable estimation in this topic. Moreover, very limited evidence in Asian population warrants an importance of findings in this study in planning of cancer prevention.

In last several decades, average BMI in Japanese population increased constantly [2, 3], although proportion of obesity has been low compared with Western populations. Taken concrete association between colorectal cancer risk and BMI in this study, constant BMI increase in Japanese population over decades is one of the unequivocal reasons for rapid increase on colorectal cancer incidence in Japan observed until early 1990s [30]. In other words, reducing burden of excess BMI in Japanese population can prevent substantial proportion of colorectal cancer.

PAF is one of the indicators for proportion of preventable fraction in certain population. In this study, PAFs by BMI ≥25 kg/m^2 were revealed to be 3.6% for males and 2.6% for females, indicating that potential quantitative impacts of reducing BMI <25 on colorectal cancer in Japanese population. This is smaller than those estimated in Western population [31]. Renehan et al. recently estimated PAF of BMI ≥25 kg/m^2 on colon (10.92% for males and 2.57% for females) and rectal cancer (5.05 for males) by using data of 30 countries in Europe. This difference might be reasonable because there is large difference in prevalence of obesity or overweight between Japanese and Western population [1–3] because HRs for 5 kg/m^2 BMI increase in Western populations (1.23 for North American population and 1.13 in European population) [14] are almost comparable with our finding in this pooled analysis (1.16 for 5 kg/m^2 increase). Considering a rapid increase in the proportion of overweight and obesity in Asian population [1], we may imagine the increase of colorectal cancer burden in Asia in near future. That is to say expected increase of colorectal cancer will be prevented if the appropriate program for obesity will be applied.

The present study has several strengths. It included most of the ongoing, large-scale prospective cohorts in Japan. Total numbers of subjects in this analysis is very large warranting statistical power to detect association between BMI and colorectal cancer risk. In addition, the birth generation of the study subjects in the cohorts overlapped. Therefore, pooling of these cohorts allows for stable summary quantitative estimates of the effect of BMI on premature death in middle-aged and elderly Japanese adults. The use of incidence rather than mortality as an end point is advantageous enabling directly referring risk contribution by BMI. At the same time, because this study was not based on a meta-analysis of published studies, the possibility of publication bias is small. In the studies included in this pooled analysis, BMI was measured before colorectal cancer incidence, which precludes the possibility of selection and recall bias. Most of the studies used validated questionnaires or equivalent ones for BMI measurement; therefore, impact of error in the analysis can be limited if it exists. In addition, the categories for BMI and the covariates used were identical across study, which removes a potential source of heterogeneity that can occur when conducting a meta-analysis of published studies.

However, there are several limitations that warrant consideration. We observed significant heterogeneity of association in colorectal cancer in men. Although we applied random effects model, an effect of this on summary estimates can be undeniable. As our analyses were conducted using only a baseline questionnaire, we were unable to consider changes over time in BMI. Similar is true to change of potential confounders in the analysis. Although we considered potential confounders in the analysis, potential residual confounding cannot be completely ruled out. Lastly, we estimated PAFs based upon distribution of BMI within cohorts in this analysis. Assuming potential selection bias of subjects in the studies pooled, our PAFs estimated in this analysis could be under/overestimated ones. Therefore, PAFs should be carefully interpreted.

In conclusion, we found a positive and a significant association between BMI and colorectal cancer risk by pooling of data from cohort studies with considerable number of subjects among Japanese population. This association was stronger in colon, especially in proximal colon, relative to rectum. Males showed stronger association than females. This information is important in cancer control planning by prevention of obesity especially in Asian population.

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disclosure

The authors have declared no conflicts of interest.